

## Review Article



*Making Nutrition a Development Priority in Africa*

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## Bioactive molecules of grape

Farida Benmezziane \*

Department of Agricultural Sciences, Laboratory of animal health, plants production, environment and food safety. University of Chadli Bendjedid, El-Tarf. PB 73. El-Tarf 36000. Algeria

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### ABSTRACT

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#### \* Corresponding author info:

Farida Benmezziane  
Tel. (+213) 775613108  
Email: [benmezzianefarida@yahoo.fr](mailto:benmezzianefarida@yahoo.fr)

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The aim of this review article is to provide literature on the grape antioxidants. A very thorough literature search was conducted to describe the bioactive molecules of grapes with antioxidant power. Grape, fruit of wide culture, is very consumed and especially appreciated by the populations of North Africa (Algeria, Morocco, and Tunisia). Grape is a very energetic and refreshing fruit, so it is recommended for the feeding of children and athletes. Not only grape is a tonic provider, but it is also very nutritious because of the elements it contains, such as vitamin C and many group B vitamins. Moreover, grape contains several bioactive molecules with antioxidant character, which have beneficial effects for the human health. Many studies have also shown its effects following the frequent consumption of grapes or grape juice.

**Keywords:** Grape, bioactive molecules, antioxidant, health.

## 1 Introduction

Historically, men have always drawn from nature what to feed, to dress and to treat themselves. Four out of five people use plants to ward off their ills. In Africa, up to 80% of the population uses traditional medicine to treat themselves. Many studies indicated that people having a rich diet in fruits and vegetables suffer less from diseases related to aging like Alzheimer [1-4]. Today, consumers are not interested in the amount of food they consume, but rather on their beneficial effect on health. The detrimental effects of industrial food processing, excessive

use of preservatives, and food additives are known well established. So, fruits and vegetables represent symbols of a healthy lifestyle due to their several benefits linked to their low-calorie content, high fiber, minerals, vitamins, and other micronutrients content [5-7]. Furthermore, fruits and vegetables constitute an important source of antioxidants, such as phenolic compounds [8] whose effectiveness is recognized for both human health and the agrifood industry. Among these fruits, the grape, highly cultivated fruit as well in Algeria as in Morocco, and in Tunisia. Grape is extremely esteemed because of its delicious and sweet taste, its nutritional density, and

especially its content of antioxidant compounds (polyphenols, flavonoids, and carotenoids, etc.) [9]. Grapes that have the form of bunches, from which the name derives, are made of many grains, which are botanically berries, more or less small and light in color; white grape (yellow-green, or golden yellow), or darker; red grapes (red, black-purple). Grapes are consumed as fresh fruit, table grape (Cardinal, Gros noir, Muscat blanc, etc.), dried, used especially in pastry or cooking, or consumed as juice [10]. Some of grape compounds possess antioxidant properties, that remarkably beneficial for human health as protector against free radicals and some chronic diseases such as: cancer, cardiovascular diseases, and other metabolic pathologies. Moreover, it was found that they could reduce the risk of thrombosis and atherosclerosis [11, 12]. Grape composition has been widely studied by several authors, although most compounds are still unknown [13-15]. This constitutes the aim of the current review article which provides an overview of grape content in bioactive molecules identified so far.

## 2 Non-phenolic compounds

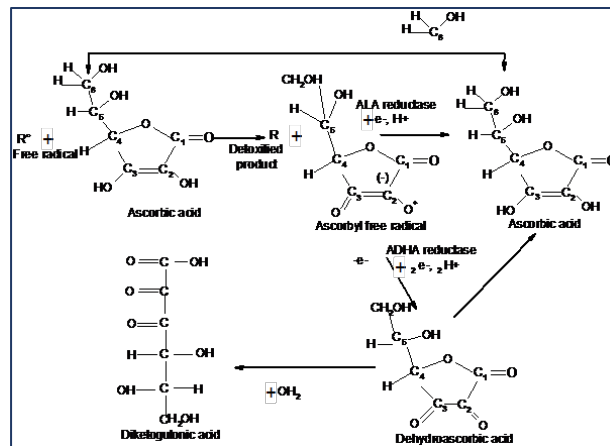
The non-phenolic compounds are elements whose structure does not respond to that of polyphenols, but they have considerable antioxidant activity as phenolic compounds.

### 2.1 Ascorbic acid (Vitamin C)

Ascorbic acid is an essential nutrient which is provided, exclusively, by vegetables and fruits. Vitamin C exists in reduced form, ascorbic acid, and in oxidized form, dehydroascorbic acid. The couple ascorbic acid/dehydroascorbic acid allows the transfer of one or two electrons; therefore, vitamin C is involved in many reactions. The antioxidant effect of ascorbic acid may be direct by free radical inhibition or indirect by tocopherols regeneration:

#### - Free radicals' inhibition

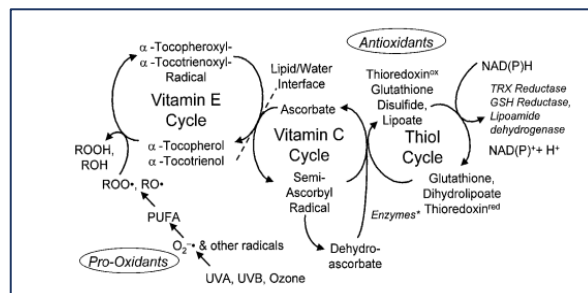
Ascorbic acid is a good scavenger for oxidizing species such as singlet oxygen ( $^1O_2$ ) and peroxy radical ( $ROO^\bullet$ ). The free radical ( $R^\bullet$ ) is neutralized by the transfer of an electron from ascorbic acid (AA), it results in a detoxified product (R) and an ascorbyl free radical (RLA). The reaction between two molecules of the RLA leads to the production of ascorbic acid and dehydroascorbic acid (ADHA), a molecule that can be converted into ascorbic acid by ADHA reductase or into a stable compound, diketogulonic acid (Figure 1) [16].



**Figure 1:** Ascorbic acid action on a free radical and the ways of its regeneration [16]

#### - Tocopherols' Regeneration

Ascorbic acid is a water-soluble vitamin that can react outside the cell membrane with the free radicals of the aqueous medium [16]. By interaction with a radical  $R^\bullet$ , the tocopherol is transformed into a tocopheryl radical. This latter is regenerated into tocopherol by the action of an ascorbic acid which, in turn, takes a radical form (ascorbyl radical). Reduced glutathione (GSH) allows the regeneration of ascorbic acid by transforming into a thyl radical ( $GS^\bullet$ ) which, by reaction with itself, gives the oxidized glutathione (GSSG) (Figure 2) [17].



**Figure 2:** Tocopherols regeneration via the ascorbic acid action [17]

### 2.2 Carotenoids

Carotenoids, fat-soluble pigments, are responsible for the yellow, red, and orange colors of fruits and vegetables. These pigments belong to the family of tetraterpenoid (C40) formed of linked eight isoprenic units (C5) and form a symmetrical molecule [18]. This skeleton can be modified by:

- Cyclization at one end or at both ends of the molecule to obtain different end groups;
- Changes in hydrogenation levels;
- And oxygen supply containing functional groups [19].

### Structure

There are two main classes of carotenoids:

#### a. Carotenes

Carotenes ( $\beta$ -carotene,  $\alpha$ -carotene, phytofluene, phytoene, etc.) present hydrocarbonyl chains with a high number of conjugated bounds, which gives them a color varying from yellow to red [18].

#### b. Xanthophylls

They are more polar than carotenes and contain oxygen atoms in their structure (lutein, zeaxanthin, violaxanthin, etc.) [18].

The main carotenoids (85% of the total carotenoids) identified in the grapes are  $\beta$ -carotene and lutein, as shown on Figure 3. The rest being neochrome, neoxanthin, violaxanthin, luteoxanthin, flavoxanthin, zeaxanthin, and isomers -cis of lutein and  $\beta$ -carotene. Carotenoids are directly involved in the grape aroma, undergoing degradation which leads to the apparition of norisoprenoids compounds known for their aromatic power [21].

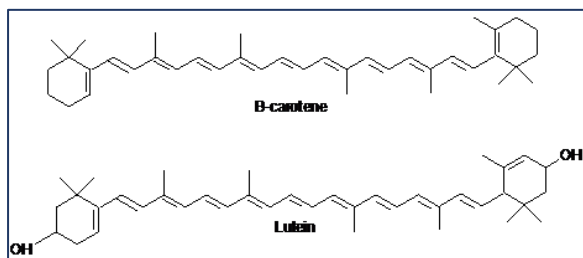
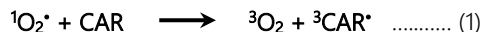


Figure 3: Chemical structures of main grape carotenoids [20]

### Antioxidants properties

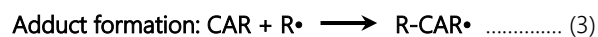
The antioxidants properties of carotenoids are attributed to their ability to scavenge singlet oxygen and free radicals. The main mechanism of carotenoids photoprotection against singlet oxygen ( $^1O_2$ ) is the transfer of electronic energy. However, these chemical reactions can lead to the destruction of carotenoids [19]. Once produced,  $^3CAR^*$  can easily return to the ground state dissipating the energy as heat or it can be quenched physically via enhanced intersystem crossing by  $^3O_2$ . Thus, the carotenoids act as catalysts deactivating  $^1O_2$  [19].



According to Dutta *et al* [19], the carotenoids can react with free radicals via the following mechanisms:

- **Electron transfer:** the oxidation of radical with a high redox potential can release an electron from carotenoid molecule to give a cation radical ( $CAR^{\bullet+}$ );
- **Adduct formation:** carotenoids react with free radicals and give stable radical complexes;

- **Hydrogen transfer:** carotenoids can inhibit free radicals by hydrogen transfer, thus forming a  $CAR^*$  radical.



## 3 Phenolic compounds

Polyphenols or phenolic compounds are important constituents of grapes. These are products of the plants' secondary metabolism. From a chemical point of view, the phenolic compounds are characterized by the presence of an aromatic nucleus carrying one or more hydroxyl groups; they can be divided into two groups: (i) phenolic acids and associated compounds, commonly called non-flavonoids and (ii) flavonoids [22].

### 3.1 Non-flavonoid compounds

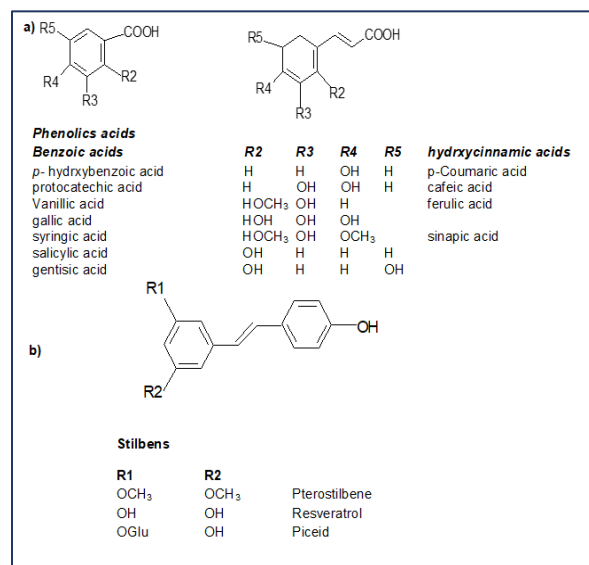
The non-flavonoid compounds include phenolic acids, divided into hydroxybenzoic acids and hydroxycinnamic acids, carrying an unsaturated side chain. Other phenolic derivatives such as stilbenes (resveratrol, piceid) of structure C6-C2-C6 exist too. They have not flavone skeleton, these are the main non-flavonoids of food importance.

#### Phenolic acids

The majority of phenolic acids of grapes are:

- **Hydroxycinnamic acids:** characterized by a C6-C3 carbon skeleton (Figure 4). Cinnamic acid is produced by phenylalanine deamination, a reaction catalyzed by the phenylalanine Amonia-Lyase (PAL), para-coumaric acid (*p*-coumaric) is then produced by hydroxylation of cinnamic acid. Cinnamic acid and hydroxycinnamic acids are also called phenylpropanoids. Their basic skeleton is a benzene ring with a 3-carbon aliphatic chain, with one or more hydroxyl groups often esterified to the aliphatic alcohol ester. They include *p*-coumaric acid, caffeic acid, ferulic acid, and sinapic acid. They are produced by series of hydroxylation and methylation and they often accumulate in the form of tartaric acid esters: coutaric, caftaric, and fertaric acids, respective esters of *p*-coumaric, ferulic, and sinapic acids. The major compound of the hydroxycinnamic acids in grape is the caftaric acid (caffeoyl-tartaric ester).
- **Benzoic acids:** they present a C6-C1 carbon skeleton composed of a benzene ring on which an aliphatic chain is attached to a carbon (Fig. 4). Vanillic, syringic, gentisic, and gallic acid are identified. They are found

in free form or esterified by flavanols. In grapes, gallic acid is the most abundant in seeds [23]. The natural form is *trans* (E) but *cis* (Z) isomers exist in small quantities [25].



**Figure 4:** (a) Structure of grape phenolic acids and (b) Chemical structures of some grape stilbene [23, 24]

### Stilbenes

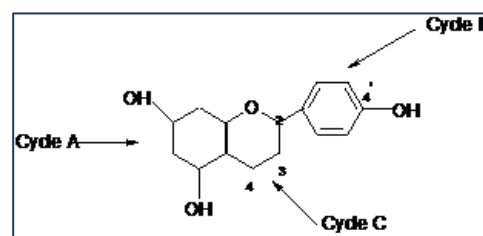
Stilbenes (1,2 diarylméthylène) are phenolic compounds with a C6-C2-C6 structure, two benzene rings linked by a methylene bridge. There is much research about this group of compounds, especially on resveratrol (3,5,4'-trihydroxystilbene) as shown on Figure 4; essentially for its antiradical properties and its implication on the pharmaceutical and medicinal aspects. Usually, stilbenes participate in the resistance of plant tissues to fungal attack, especially to *Botrytis cinerea*. Resveratrol is synthesized by the condensation of 4-coumaryl, and 3 malonyl CoA, each given 2 carbon atoms. This reaction is catalyzed by stilbene synthase (EC 2.3.1.95). UV light with a short wavelength (254 nm) can also induce the formation of resveratrol in grape leaves or grape berries [26]. Stilbenes are present in much smaller amounts than flavonols [27]. Resveratrol is in *cis* and *trans* form and is present in plant tissues, primarily as *trans*-resveratrol-3-O-glucoside [23].

According to Jeandet *et al.* [26], stilbenes, which are synthesized following the phenylalanine/polymalonat way, accumulate rapidly in grape tissues adjacent to *Botrytis cinerea*-infected zones. However, some results indicate that, in grape, changes in phytoalexin production potential depend on the physiological stage of the plant; the ability of *Vitis vinifera* (Pinot Noir) grape skin cells to synthesize resveratrol decreases abruptly at maturation

stage, which is also demonstrated in Moriarty *et al.* studies [28].

### 3.2 Flavonoid compounds

Flavonoids, the most important class of polyphenols, constitute a large family of phenolic compounds having a common C6-C3-C6 structure of the phenyl-2-benzopyran type. They include two benzene rings linked by an oxygen-containing a pyrene ring (Figure 5). Some of them contribute to very bright colors of flowers, fruits, and sometimes leaves. They are found at the level of plant cells vacuoles and are divided into several sub-families distinguished by oxidation degree of and substitution in positions 3 and 4 of the pyranic cycle C. There are about a dozen recognized classes of flavonoids, the main ones being flavones, flavonols, flavan-3-ols, isoflavones, flavanones and anthocyanidins [29]. It should be noticed that isoflavones are not present in grapes. Anthocyanins, flavonols, and flavan-3-ols are the main flavonoids found in *Vitis vinifera* grapes. The antioxidant activity of flavonoids has already been demonstrated about 40 years ago. Their antioxidant activity depends on the reactivity of the hydroxyl substituents in hydrogen atom transfer reactions [30].



**Figure 5:** The basic skeleton of flavonoids [24]

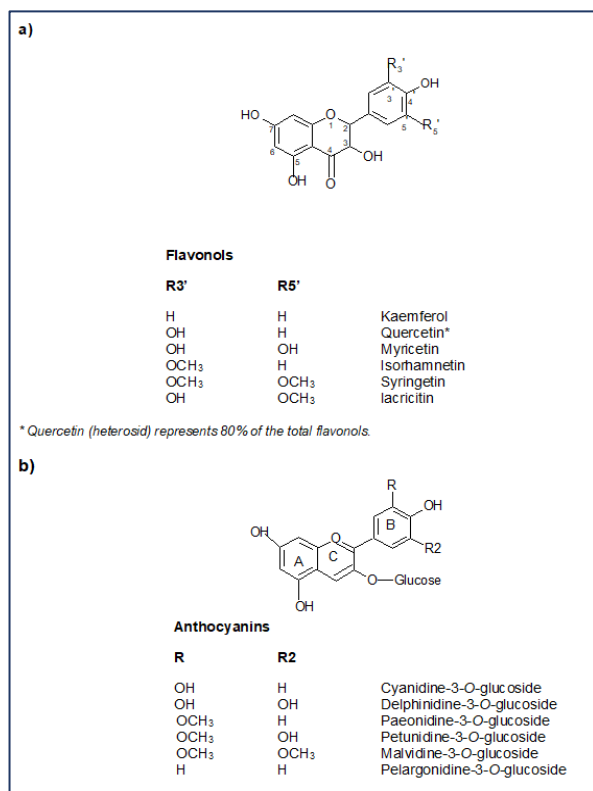
### Flavonols

In the grape berry, flavonols, pale yellow pigments, are products of flavonoids biosynthesis pathway, which also gives rise to anthocyanins and condensed tannins; they are present only in berry skin. They exist as glycosides in position 3, generally glucosylated. Furthermore, there are significant amounts of glucuronides too. Four glycosylated flavonols, derived from four aglycones, are predominantly present in grapes (kaempferol, quercetin, myricetin, and isorhamnetin) (Figure 6). Syringetin and laricitin derivatives have recently been found in red varieties according to the work of Mattivi *et al.* [31].

### Anthocyanins

Anthocyanins (from the Greek anthos = flower and kyanos = blue) are water-soluble pigments that stain petals, seed teguments, fruits and leaves in various shades of red, purple and black. They are ubiquitous components of

foods and beverages to which they communicate their color. Due to their dyeing properties and their safety, anthocyanins have been accepted as food colors (E163) [32]. Anthocyanins accumulate in the vacuoles of skin berries of black grapes' hypodermic cells, when white grapes are lacking. These compounds are involved in plant protection (absorbance in the UV). Anthocyanins of the genus *Vitis vinifera* are cyanidin-3-O-glucoside, delphinidin-3-O-glucoside, paeonidine-3-O-glucoside, petunidin-3-O-glucoside, and malvidin-3-O-glucoside (Figure 6) which is the predominant anthocyanin, although the relative composition of anthocyanins varies according to grape variety [33].



**Figure 6:** (a) Aglycone structure of grape flavonols and (b) Structure of the main grape anthocyanins

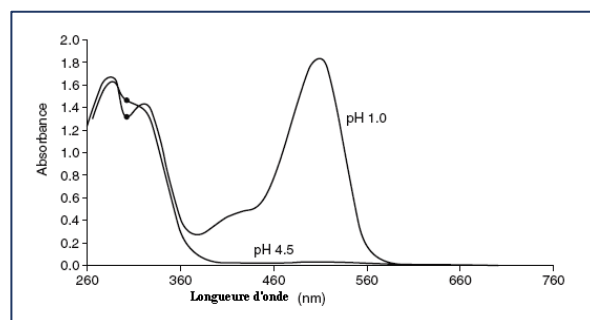
#### Equilibrium of anthocyanins according to pH

Anthocyanins color depends on their chemical structure and on their physicochemical environment in which they are found too. pH represents one of the main factors influencing color, according to which four equilibrium forms coexist in an aqueous medium, which are manifested by different absorbance spectra (Figure 7). According to Antal *et al.* [32], in an acidic medium (pH 1-3), the color of anthocyanins is determined by the hydroxylation degree of B cycle, producing a bathochromic effect (the color becomes darker), while

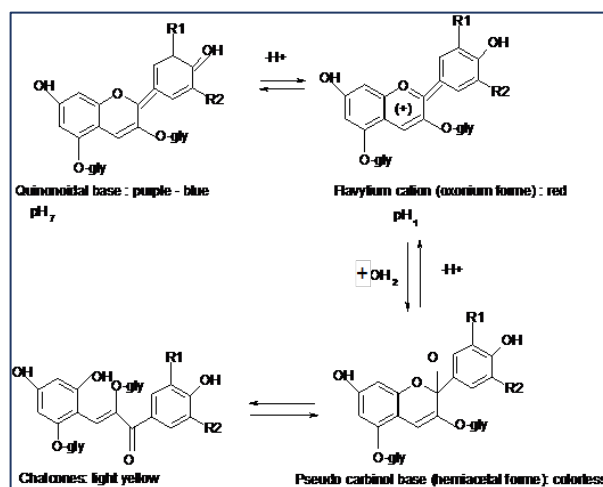
methylation at the 3' and 5' positions (R, R2) gives a hypsochromic effect (the color becomes lighter). Four forms of anthocyanins coexist according to medium pH (Figure 8):

- The flavylium A + cation of red color;
- The quinone bases AO of blue-mauve color;
- The pseudo bases or AOH carbinol bases are colorless;
- And the Cis and Trans C chalcones, light yellow in color.

Between pH 3.0 and 4.0, the predominant forms of anthocyanins are the colorless forms AOH. They represent between 65 and 85% of all anthocyanins. The flavylium A+ red form represents, on this same pH range, between 4 and 28% of anthocyanins. AO forms represent an important part of the overall color intensity too, since they constitute between 2 and 5% of total anthocyanins. At pH 4, they represent the bulk of chromophores, the chalcone forms being weakly colored [35].



**Figure 7:** Absorbance spectrum of purified red anthocyanins in buffer solutions pH 1.0 and pH 4.5 [34]



**Figure 8:** Structural forms of predominant anthocyanins at different pH [34]

### Condensed tannins or proanthocyanidins (flavan-3-ols)

Condensed tannins, also called proanthocyanidins, are polymers of flavanols. They are widely used in our diet (fruits, tea, etc.) and play a key role in the organoleptic and nutritional qualities of the products. In grapes, flavanols are either in form of monomers or polymers creating the condensed tannins in the hypodermic layers of the skin and the soft parenchyma of seeds between the cuticle and the hard seed coat [27, 36-37]. In grape berry, tannins are concentrated in the skin and seed [38, 39]. Their complex structure is composed of monomeric repeating units varying by their asymmetric carbons, their degree of oxidation, and their number of galloylated substituents [40]. The tannins of the seed are procyanidins, partially galloylated, based on catechin, epicatechin, and 3-O-gallate epicatechin units, linked together by C4-C6 or C4-C8 bonds. Skin tannins also include prodelphinidin and have lower gallate proportions than seed tannins [25]. The average degrees of polymerization are in order of 10 in the seeds and 30 in the skins. The concentration of tannins is higher in seeds than in skins, but for wines, the contribution of skins to all tannins in the berry sometimes exceeds that of seeds [25]. The study conducted by Nunez *et al.* [41] shows that the distribution of flavan-3-ols is generally determined by genetic factors and is also influenced by climatic conditions.

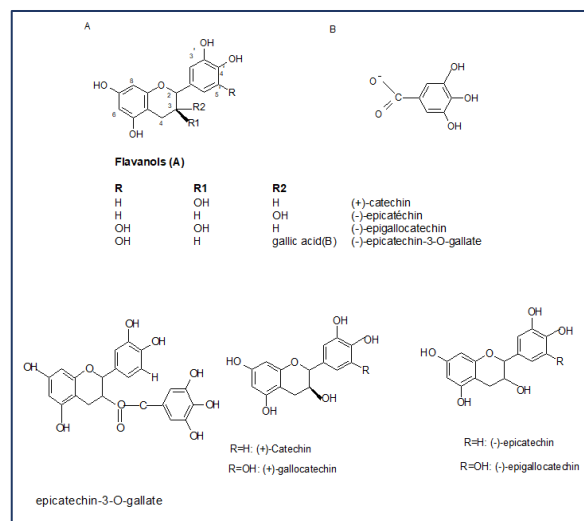
### Monomeric units

The monomeric forms of flavanols are differentiated by the stereochemistry of asymmetric C-2 and C-3 carbons, the presence of galloyl substituents, and the hydroxylation level of B ring (Figure 9). Dihydroxylated forms (catechin family) and trihydroxylated forms (galocatechins family) are thus distinguished. The latter has not been identified in grape in their monomeric forms, but their presence in polymeric forms, especially in the skins and pulp of *Vitis vinifera*, suggests their existence as monomers [27, 40]. These units may be substituted by gallic acid at the C-3 position, in particular, epicatechin, forming epicatechin-3-O-gallate (Figure 9) [25].

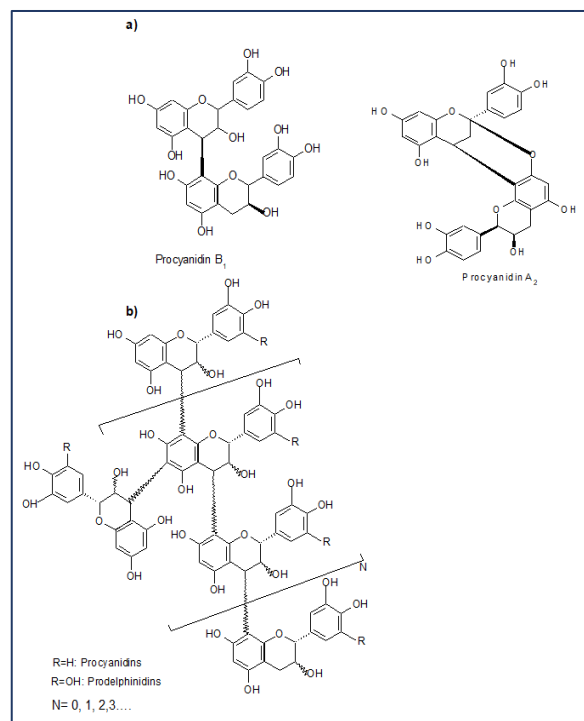
### Condensed tannins (type A and B)

The condensed tannins or proanthocyanidins are oligomers or polymers of flavan-3-ols which have the property to release, in hot acidic medium, anthocyanins by breaking the intermonomeric bond (Bate-Smith reaction) [43]. In grapes, depending on the nature of the released anthocyanin, there are two types of proanthocyanidins: Procyanidins (catechin and epicatechin polymers), and prodelphinidins (galocatechin and epigallocatechin polymers), which, by hydrolysis, release cyanidin and delphinidin respectively (Figure 9)

[44]. The procyanidins structure depends, not only on flavan-3-ols, but on the degree of polymerization and the position of the bond between these units too. Depending on the position of this bond, two proanthocyanidins' types are distinguished A and B; type B is characterized by a bond that can be either C4-C8 or C4-C6, while, type A contains an additional C2-O-C or C-O-C5 ether linkage of A ring. The following figure shows an example of each type (Figure 10 (a)) [44].



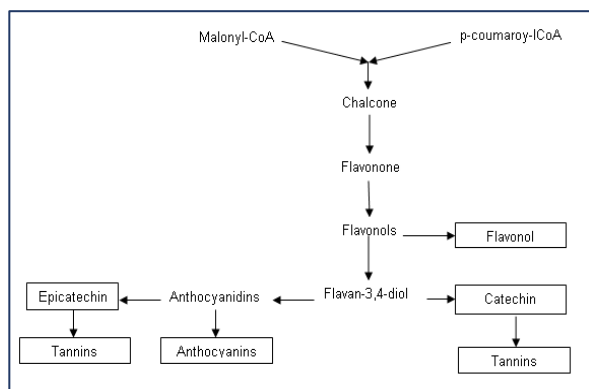
**Figure 9:** Chemical structure of some monomeric units of condensed tannins [24, 42]



**Figure10:** (a) Some grape proanthocyanidins (Type B and A); (b) General structure of proanthocyanidins

Proanthocyanidins or flavan-3-ols present in the grapes are mainly found in the form of polymers (60-80%), followed by the oligomeric forms (15-30%), whereas the flavan-3-ols monomers (catechins) are present in a smaller proportion (less than 10%) [35]. Seed tannins consist mainly of partially galloylated procyanidins [27], while those of the skin contain, in addition prodelphinidins, which makes the major difference between these two compartments of grape. The average number of monomeric units, defined as the mean degree of polymerization (DPM), can range up to 18 in a seed fraction and is close to 83 units in a skin extract [40-41, 43]. Figure 10 (b) illustrates the general structure of proanthocyanidins.

According to Kennedy *et al.* [39]; Adams [27], Cadot *et al.* [37], the skin tannins, synthesized very early in the development of the bay, change slightly from the maturation to the harvest, although their concentration decreases along the growth of the berries. Qualitative changes, such as increasing of the polymerization degree, can also take place from maturation to harvest. Generally, there is a decrease in seed tannin during ripening that follows the seeds' browning, which may be due to tannins' oxidation. Sun *et al.* [45] and Ó-Marques *et al.* [46] showed that levels of catechins and proanthocyanidins vary considerably, depending on the variety, the year of harvest, and the ripening degree.



**Figure 11:** Biosynthesis pathway of the main flavonoids present in grape berries [27]

Compounds accumulated in the fruit are encircled in rectangles, the other intermediates are present at low levels

#### Location and compartmentalization of flavonoids in the grape berry

In grapes, the different flavonoids have a different spatiotemporal location. Flavan 3-ols are accumulated mainly in the seed and skin [39], and in very small amounts in the pulp [47]. Flavonols are only present in the skin [48, 49]. As for the anthocyanins, they are located exclusively

in the skin of red grape varieties. In the case of grape varieties known as "dyers", there is also an accumulation of anthocyanins in the pulp. The flavan 3-ols are synthesized in the skin during the herbaceous phase and in the seeds, their accumulation continues until about a week after maturation [50]. Flavonols are accumulated in two stages: a first phase of synthesis just after flowering and a second period of synthesis which starts with maturation and continues during all the maturation [49]. The accumulation of anthocyanins starts only from the maturation and continues until maturity [48]. This accumulation is concomitant with that of sugars in the pulp [50]. Figure 11 illustrates the biosynthetic pathway of the main flavonoids present in grape berries.

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